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(54) Integrated delivery device for continuous glucose sensor

(57) A method for treating diabetes with an integrated glucose sensor and medicament delivery device, the method comprising:
receiving sensor data from a glucose sensor, the sensor data comprising one or more sensor data points;
calculating a medicament therapy recommendation based at least in part on the sensor data;
validating the calculated therapy recommendation based on data input into a receiver, data obtained from a single point glucose monitor, or combinations thereof; and
outputting information reflective of the calculated therapy recommendation responsive to a validated calculated therapy recommendation.

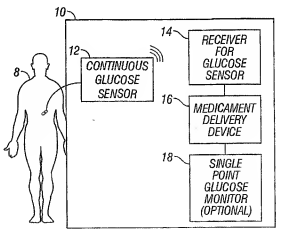

FIG. 1

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Description

Field of the Invention

[0001] The present invention relates generally to systems and methods monitoring glucose in a host. More particularly, the present invention relates to an integrated medicament delivery device and continuous glucose sensor.

Background of the Invention

[0002] Diabetes mellitus is a disorder in which the pancreas cannot create sufficient insulin (Type I or insulin dependent) and/or in which insulin is not effective (Type 2 or non-insulin dependent). In the diabetic state, the victim suffers from high blood sugar, which may cause an array of physiological derangements (for example, kidney failure, skin ulcers, or bleeding into the vitreous of the eye) associated with the deterioration of small blood vessels. A hypoglycemic reaction (low blood sugar) may be induced by an inadvertent overdose of insulin, or after a normal dose of insulin or glucose-lowering agent accompanied by extraordinary exercise or insufficient food intake.

[0003] Conventionally, a diabetic person carries a self-monitoring blood glucose (SMBG) monitor, which typically comprises uncomfortable finger pricking methods. Due to the lack of comfort and convenience, a diabetic will normally only measure his or her glucose level two to four times per day. Unfortunately, these time intervals are so far spread apart that the diabetic will likely find out too late, sometimes incurring dangerous side effects, of a hyper- or hypo-glycemic condition. In fact, it is not only unlikely that a diabetic will take a timely SMBG value, but the diabetic will not know if their blood glucose value is going up (higher) or down (lower) based on conventional methods, inhibiting their ability to make educated insulin therapy decisions.

[0004] Home diabetes therapy requires personal discipline of the user, appropriate education from a doctor, proactive behavior under sometimes-adverse situations, patient calculations to determine appropriate therapy decisions, including types and amounts of administration of insulin and glucose into his or her system, and is subject to human error. Technologies are needed that ease the burdens faced by diabetic patients, simplify the processes involved in treating the disease, and minimize user error which may cause unnecessarily dangerous situations in some circumstances.

Summary of the Invention

[0005] In a first embodiment, a method for managing diabetes is provided, including: receiving in a receiver a data stream from an integrated glucose sensor, the data stream including at least one sensor data point; calculating a medicament therapy recommendation responsive to the into the receiver and data obtained from an integrated single point glucose monitor to yield an assessment result; and outputting information based on the assessment result, wherein the information is employed in the management of diabetes.

[0006] In an aspect of the first embodiment, the output step includes outputting the medicament therapy recommendation to a user interface after confirmation of a therapy decision by a user when the assessment result is indicative of a failed validation.

[0007] In an aspect of the first embodiment, the output step includes outputting the medicament therapy recommendations to a user interface when the assessment result is indicative of a successful validation.

[0008] In an aspect of the first embodiment, the output step includes displaying the medicament therapy recommendation on at least one of a receiver and a medicament delivery device user interface.

[0009] In an aspect of the first embodiment, the output step includes transmitting the medicament therapy recommendation to a medicament delivery device.

[0010] In an aspect of the first embodiment, the output step includes delivering a medicament according to the medicament therapy recommendation via an automated delivery device.

[0011] In a second embodiment, a method for managing diabetes in a host is provided, including: receiving in a receiver medicament delivery data responsive to medicament delivery from a medicament delivery device; receiving in a receiver a data stream from an integrated glucose sensor, the data stream including at least one sensor data point obtained before the medicament delivery or after the medicament delivery; determining a metabolic response of the host to the medicament delivery; receiving a subsequent data stream from the integrated glucose sensor, the data stream comprising at least one subsequent sensor data point; and calculating a medicament therapy recommendation responsive to the host's metabolic response to the medicament delivery, wherein the medicament therapy recommendation is employed in managing diabetes in the host.

[0012] In an aspect of the second embodiment, the metabolic response is calculated using a pattern recognition algorithm.

[0013] In an aspect of the second embodiment, the step of determining a metabolic response is repeated when the receiver receives additional medicament delivery data.

[0014] In an aspect of the second embodiment, the metabolic response is iteratively determined for a time period exceeding one week.

[0015] In a third embodiment, a method for estimating a glucose level is provided, including: receiving in a receiver a data stream from an integrated glucose sensor, the data stream responsive to a medicament delivery from a medicament delivery device; determining a metabolic response of a host associated with the medicament delivery by evaluating the medicament delivery data using glucose sensor data correlated with times of delivery and release of the medicament delivery; and estimating a glucose level responsive to the metabolic response associated with the medicament delivery.

[0016] In an aspect of the third embodiment, the metabolic response is calculated using a pattern recognition algorithm.

[0017] In an aspect of the third embodiment, the step of determining a metabolic response is repeated when additional medicament delivery data is received by the receiver.

[0018] In an aspect of the third embodiment, the metabolic response is iteratively determined for a time period exceeding one week.

[0019] In a fourth embodiment, an integrated system for monitoring and treating diabetes is provided, including: a glucose sensor, wherein the glucose sensor is configured to substantially continuously measure glucose in a host, and is configured to output a data stream, including at least one sensor data point; a receiver operably connected to the glucose sensor, wherein the receiver is configured to receive the data stream; and a medicament delivery device, wherein the delivery device is at least one of physically connected to the receiver and operably connected to the receiver.

[0020] In an aspect of the fourth embodiment, the glucose sensor includes an implantable glucose sensor.

[0021] In an aspect of the fourth embodiment, the glucose sensor includes a long-term subcutaneously implantable glucose sensor.

[0022] In an aspect of the fourth embodiment, the medicament delivery device includes a syringe detachably connectable to the receiver.

[0023] In an aspect of the fourth embodiment, the medicament delivery device includes at least one transdermal patch detachably connectable to the receiver.

[0024] In an aspect of the fourth embodiment, the medicament delivery device includes an inhaler delivery device or a spray delivery device, wherein the delivery device is detachably connectable to the receiver.

[0025] In an aspect of the fourth embodiment, the medicament delivery device includes a pen-type or a jet-type injector.

[0026] In an aspect of the fourth embodiment, the medicament delivery device includes a transdermal pump.

[0027] In an aspect of the fourth embodiment, the medicament delivery device includes an implantable pump. includes a manual implantable pump.

[0028] In an aspect of the fourth embodiment, the medicament delivery device includes a cell transplantation device.

[0029] In an aspect of the fourth embodiment, the medicament delivery device is detachably connected to the receiver.

[0030] In an aspect of the fourth embodiment, the medicament delivery device is operably connected to the receiver by a wireless connection.

[0031] In an aspect of the fourth embodiment, the medicament delivery device is operably connected to the receiver by a wired connection.

[0032] In an aspect of the fourth embodiment, further including a single point glucose monitor, wherein the single point glucose monitor is at least one of physically connected to the receiver and operably connected to the receiver.

[0033] In an aspect of the fourth embodiment, the glucose sensor includes an enzyme membrane system for electrochemical detection of glucose, and wherein the single point glucose monitor includes an enzyme membrane system for electrochemical detection of glucose.

[0034] In an aspect of the fourth embodiment, the receiver includes a microprocessor, and wherein the microprocessor includes programming for calculating and outputting medicament delivery instructions

[0035] In an aspect of the fourth embodiment, the microprocessor further includes a validation module that validates a medicament delivery instruction prior to outputting the medicament delivery instruction.

[0036] In an aspect of the fourth embodiment, the receiver is configured to receive, for a first time period, medicament delivery data responsive to medicament delivery from the medicament delivery device.

[0037] In an aspect of the fourth embodiment, the receiver includes a microprocessor, and wherein the microprocessor includes programming to determine a metabolic response of a host to medicament delivery for the first time period by evaluating a sensor data point substantially corresponding to a time of delivery or release of the medicament to the host.

[0038] In an aspect of the fourth embodiment, the microprocessor calculates a medicament therapy recommendation for a second time period responsive to the sensor data and the metabolic response.

[0039] In an aspect of the fourth embodiment, the microprocessor includes programming to estimate a glucose value responsive to glucose sensor data and a metabolic response of a host.

substantially continuously measure glucose in a host for a time period exceeding one week.

[0040] In another aspect of the fourth embodiment, the glucose sensor is configured to substantially continuously measure glucose in a host for a time period from about two days to about one week.

Brief Description of the Drawings

[0041] Fig. 1 is a block diagram of an integrated system of the preferred embodiments, including a continuous glucose sensor, a receiver for processing and displaying sensor data, a medicament delivery device, and an optional single point glucose-monitoring device.

[0042] Fig. 2 is a perspective view of a continuous glucose sensor in one embodiment.

[0043] Fig. 3 is a block diagram of the electronics associated with a continuous glucose sensor in one embodiment.

[0044] Figs. 4A and 4B are perspective views of an integrated system 10 in one embodiment, wherein a receiver is integrated with a medicament delivery device in the form of a manual syringe, and optionally includes a single point glucose monitor.

[0045] Figs. 5A to 5C are perspective views of an integrated system in one embodiment, wherein a receiver is integrated with a medicament delivery device in the form of one or more transdermal patches housed within a holder, and optionally includes a single point glucose monitor.

[0046] Figs. 6A and 6B are perspective views of an integrated system in one embodiment, wherein a receiver is integrated with a medicament delivery device in the form of a pen or jet-type injector, and optionally includes a single point glucose monitor.

[0047] Figs. 7A to 7C are perspective views of an integrated system in one embodiment, wherein a sensor and delivery pump, which are implanted subcutaneously or transdermally inserted into the patient, are operably connected to an integrated receiver, and optionally include a single point glucose monitor.

[0048] Fig. 8 is a block diagram that illustrates integrated system electronics in one embodiment.

[0049] Fig. 9 is a flow chart that illustrates the process of validating therapy instructions prior to medicament delivery in one embodiment.

[0050] Fig. 10 is a flow chart that illustrates the process of providing adaptive metabolic control using an integrated sensor and medicament delivery device in one embodiment.

[0051] Fig. 11 is a flow chart that illustrates the process of glucose signal estimation using the integrated sensor and medicament delivery device in one embodiment.

[0052] The following description and examples illustrate some embodiments of the disclosed invention in detail. Those of skill in the art will recognize that there are numerous variations and modifications of this invention that are encompassed by its scope. Accordingly, the description of a certain exemplary embodiment should not be deemed to limit the scope of the present invention.

Definitions

[0053] In order to facilitate an understanding of the preferred embodiments, a number of terms are defined below.

[0054] The term "continuous glucose sensor," as used herein, is a broad term and are used in its ordinary sense, including, but not limited to, a device that continuously or continually measures glucose concentration, for example, at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes, or longer. Continual or continuous glucose sensors can continually measure glucose concentration without requiring user initiation and/or interaction for each measurement, such as described with reference to U.S. Patent 6,001,067, for example.

[0055] The phrase "continuous glucose sensing," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, the period in which monitoring of plasma glucose concentration is continuously or continually performed, for example, at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes, or longer.

[0056] The term "biological sample," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, sample of a host body, for example, blood, interstitial fluid, spinal fluid, saliva, urine, tears, sweat, or the like.

[0057] The term "host," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, mammals such as humans.

[0058] The term "biointerface membrane," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a permeable or semi-permeable membrane that can include two or more domains and is typically constructed of materials of a few microns thickness or more, which can be placed over the sensing region to keep host cells (for example, macrophages) from gaining proximity to, and thereby damaging the sensing membrane or forming a barrier cell layer and interfering with the transport of glucose across the tissue-device interface.

[0059] The term "sensing membrane," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a permeable or semi-permeable membrane that can be comprised of two or more domains and is typically constructed of materials of a few microns thickness or more, which are permeable to oxygen and are optionally permeable to glucose. In one example, the sensing membrane comprises an immobilized glucose oxidase enzyme, which enables an electrochemical reaction to occur to measure a concentration of glucose.
sense, including, without limitation, regions of a membrane that can be layers, uniform or nonuniform gradients (for example, anisotropic), functional aspects of a material, or provided as portions of the membrane.

[0060] As used herein, the term "copolymer," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, polymers having two or more different repeat units and includes copolymers, terpolymers, tetrapolymers, and the like.

[0061] The term "sensing region," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the region of a monitoring device responsible for the detection of a particular glucose. In one embodiment, the sensing region generally comprises a nonconductive body, a working electrode (anode), a reference electrode and a counter electrode (cathode) passing through and secured within the body forming an electrochemically reactive surface at one location on the body and an electronic connection at another location on the body, and a sensing membrane affixed to the body and covering the electrochemically reactive surface. The counter electrode typically has a greater electrochemically reactive surface area than the working electrode. During general operation of the sensor a biological sample (for example, blood or interstitial fluid) or a portion thereof contacts (for example, directly or after passage through one or more domains of the sensing membrane) an enzyme (for example, glucose oxidase); the reaction of the biological sample (or portion thereof) results in the formation of reaction products that allow a determination of the glucose level in the biological sample.

[0062] The term "electrochemically reactive surface," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, the surface of an electrode where an electrochemical reaction takes place. In the case of the working electrode, the hydrogen peroxide produced by the enzyme catalyzed reaction of the glucose being detected reacts creating a measurable electronic current (for example, detection of glucose utilizing glucose oxidase produces H_2O_2 as a by product, H_2O_2 reacts with the surface of the working electrode producing two protons ($2H^+$), two electrons ($2e^-$) and one molecule of oxygen (O_2) which produces the electronic current being detected). In the case of the counter electrode, a reducible species (for example, O_2) is reduced at the electrode surface in order to balance the current being generated by the working electrode.

[0063] The term "electrochemical cell," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a device in which chemical energy is converted to electrical energy. Such a cell typically consists of two or more electrodes held apart from each other and in contact with an electrolyte solution. Connection of the electrodes to a source of direct electric current renders one of them negatively charged and the other positively charged. Positive ions in the electrolyte migrate to the negative electrode (cathode) and there combine with one or neutral atoms or molecules; at the same time, negative ions migrate to the positive electrode (anode) and transfer one or more electrons to it, also becoming new ions or neutral particles. The overall effect of the two processes is the transfer of electrons from the negative ions to the positive ions, a chemical reaction.

[0064] The term "proximal" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, near to a point of reference such as an origin or a point of attachment. For example, in some embodiments of a sensing membrane that covers an electrochemically reactive surface, the electrolyte domain is located more proximal to the electrochemically reactive surface than the interference domain.

[0065] The term "distal" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, spaced relatively far from a point of reference, such as an origin or a point of attachment. For example, in some embodiments of a sensing membrane that covers an electrochemically reactive surface, a resistance domain is located more distal to the electrochemically reactive surfaces than the enzyme domain.

[0066] The term "substantially" as used herein, is a broad term and is used in its ordinary sense, including, without limitation, being largely but not necessarily wholly that which is specified.

[0067] The term "microprocessor," as used herein, is a broad term and is used in its ordinary sense, including, without limitation, a computer system or processor designed to perform arithmetic and logic operations using logic circuitry that responds to and processes the basic instructions that drive a computer.

[0068] The term "ROM," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, read-only memory, which is a type of data storage device manufactured with fixed contents. ROM is broad enough to include EEPROM, for example, which is electrically erasable programmable read-only memory (ROM).

[0069] The term "RAM," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, a data storage device for which the order of access to different locations does not affect the speed of access. RAM is broad enough to include SRAM, for example, which is static random access memory that retains data bits in its memory as long as power is being supplied.

[0070] The term "A/D Converter," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, hardware and/or software that converts analog electrical signals into corresponding digital signals.
ordinary sense, including, but not limited to, a radio frequency transmitter and/or receiver for transmitting and/or receiving signals.

[0071] The terms "raw data stream" and "data stream," as used herein, are broad terms and are used in their ordinary sense, including, but not limited to, an analog or digital signal directly related to the analyte concentration measured by the analyte sensor. In one example, the raw data stream is digital data in "counts" converted by an A/D converter from an analog signal (for example, voltage or amps) representative of an analyte concentration. The terms broadly encompass

a plurality of time spaced data points from a substantially continuous analyte sensor, which comprises individual measurements taken at time intervals ranging from fractions of a second up to, for example, 1, 2, or 5 minutes or longer.

[0072] The term "counts," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, a unit of measurement of a digital signal. In one example, a raw data stream measured in counts is directly related to a voltage (for example, converted by an A/D converter), which is directly related to current from a working electrode.

[0073] The term "electronic circuitry," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, the components (for example, hardware and/or software) of a device configured to process data. In the case of an analyte sensor, the data includes biological information obtained by a sensor regarding the concentration of the analyte in a biological fluid. U.S. Patent Nos. 4,757,022, 5,497,772 and 4,787,398, describe suitable electronic circuits that can be utilized with devices of certain embodiments.

[0074] The term "potentiostat," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, an electrical system that controls the potential between the working and reference electrodes of a three-electrode cell at a preset value. The potentiostat forces whatever current is necessary to flow between the working and counter electrodes to keep the desired potential, as long as the needed cell voltage and current do not exceed the compliance limits of the potentiostat.

[0075] The terms "operably connected" and "operably linked," as used herein, are broad terms and are used in their ordinary sense, including, but not limited to, one or more components being linked to another component(s) in a manner that allows transmission of signals between the components. For example, one or more electrodes can be used to detect the amount of glucose in a sample and convert that information into a signal; the signal can then be transmitted to an electronic circuit. In this case, the electrode is "operably linked" to the electronic circuit. These terms are broad enough to include wired and wireless connectivity.

[0076] The term "algorithmically smoothed," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, modification of a set of data to make it a moving average of the raw data stream.

[0077] The term "algorithm," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, the computational processes (for example, programs) involved in transforming information from one state to another, for example using computer processing.

[0078] The term "regression," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, finding a line in which a set of data has a minimal measurement (for example, deviation) from that line. Regression can be linear, non-linear, first order, second order, and so forth. One example of regression is least squares regression.

[0079] The terms "recursive filter" and "auto-regressive algorithm," as used herein, are broad terms and are used in their ordinary sense, including, but not limited to, an equation in which previous averages are part of the next filtered output. More particularly, the generation of a series of observations whereby the value of each observation is partly dependent on the values of those that have immediately preceded it. One example is a regression structure in which lagged response values assume the role of the independent variables.

[0080] The terms "velocity" and "rate of change," as used herein, are broad terms and are used in their ordinary sense, including, but not limited to, time rate of change; the amount of change divided by the time required for the change. In one embodiment, these terms refer to the rate of increase or decrease in an analyte for a certain time period.

[0081] The term "acceleration" as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, the rate of change of velocity with respect to time. This term is broad enough to include deceleration.

[0082] The term "clinical risk," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, an identified danger or potential risk to the health of a patient based on a measured or estimated analyte concentration, its rate of change, and/or its acceleration.

[0083] The term "clinically acceptable," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, an analyte concentration, rate of change, and/or acceleration associated with that measured analyte that is considered to be safe for a patient.

[0084] The term "time period," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, an amount of time including a single point in time and a path (for example, range of time) that extends from a first point in time to a second point in time.

[0085] The term "measured analyte values," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, an analyte value or set of analyte values for a time period for which analyte data has been measured by an analyte sensor. The term is broad receiver (for example, data smoothing, calibration, or the like).

[0086] The term "alarm," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, audible, visual, or tactile signal that are triggered in response to detection of clinical risk to a patient. In one embodiment, hyperglycemic and hypoglycemic alarms are triggered when present or future clinical danger is assessed based on continuous analyte data.

[0087] The term "computer," as used herein, is broad term and is used in its ordinary sense, including, but not limited to, machine that can be programmed to manipulate data.

[0088] The term "modem," as used herein, is a broad term and is used in its ordinary sense, including, but not limited to, an electronic device for converting between serial data from a computer and an audio signal suitable for transmission over a telecommunications connection to another modem.

Overview

[0089] Fig. 1 is a block diagram of an integrated system 10 of the preferred embodiments, including a continuous glucose sensor 12, a receiver 14 for processing and displaying sensor data, a medicament delivery device 16, and optionally a single point glucose-monitoring device 18. The integrated diabetes management system 10 of the preferred embodiments provides improved convenience and accuracy thus affording a diabetic patient 8 with improved convenience, functionality, and safety in the care of their disease.

[0090] Fig. 1 shows a continuous glucose sensor 12 that measures a concentration of glucose or a substance indicative of the concentration or presence of the glucose. In some embodiments, the glucose sensor 12 is an invasive, minimally invasive, or non-invasive device, for example a subcutaneous, transdermal; or intravascular device. In some embodiments, the sensor 12 can analyze a plurality of intermittent biological samples. The glucose sensor can use any method of glucose-measurement, including enzymatic, chemical, physical, electrochemical, spectrophotometric, polarimetric, calorimetric, radiometric, or the like. In alternative embodiments, the sensor 12 can be any sensor capable of determining the level of an analyte in the body, for example oxygen, lactase, insulin, hormones, cholesterol, medicaments, viruses, or the like. The glucose sensor 12 uses any known method to provide an output signal indicative of the concentration of the glucose. The output signal is typically a raw data stream that is used to provide a useful value of the measured glucose concentration to a patient or doctor, for example.

[0091] Accordingly, a receiver 14 is provided that receives and processes the raw data stream, including calibrating, validating, and displaying meaningful glucose values to a patient, such as described in more detail below. A medicament delivery device 16 is further provided as a part of the integrated system 10. In some embodiments, the medicament delivery device 16 is a manual delivery device, for example a syringe, inhaler, or transdermal patch, which is manually semi-automated delivery device, for example a pen or jet-type injector, an inhaler, a spray, or pump, which provides a semi-automated integration with the receiver 14. In some embodiments, the medicament delivery device 16 is an automated delivery device, for example a transcutaneous or implantable pump system, which provides an automated integration with the receiver 14. In some embodiments, an optional single point glucose monitor 18 is further provided as a part of the integrated system 10, for example a self-monitoring blood glucose meter (SMBG), non-invasive glucose meter, or the like.

[0092] Conventionally, each of these devices separately provides valuable information and or services to diabetic patients. Thus, a typical diabetic patient has numerous individual devices, which they track and consider separately. In some cases, the amount of information provided by these individual devices may require complex understanding of the nuances and implications of each device, for example types and amounts of insulin to deliver. Typically, each individual device is a silo of information that functions as well as the data provided therein, therefore when the devices are able to communicate with each other, enhanced functionality and safety can be realized. For example, when a continuous glucose monitor functions alone (for example, without data other than that which was gathered by the device), sudden changes in glucose level are tracked, but may not be fully understood, predicted, preempted, or otherwise considered in the processing of the sensor data; however, if the continuous glucose sensor were provided with information about time, amount, and type of insulin injections, calories consumed, time or day, meal time, or like, more meaningful, accurate and useful glucose estimation, prediction, and other such processing can be provided, such as described in more detail herein. By integrating these devices, the information from each component can be leveraged to increase the intelligence, benefit provided, convenience, safety, and functionality of the continuous glucose sensor and other integrated components. Therefore, it would be advantageous to provide a device that aids the diabetic patient in integrating these individual devices in the treatment of his/her disease.

Glucose Sensor

[0093] Fig. 2 is a perspective view of one embodiment of a continuous glucose sensor 12. In this embodiment, a body 20 and a sensing region 22 house the electrodes and sensor electronics (Fig. 3). The three electrodes within the sensing region are operably connected to the sensor electronics (Fig. 3) and are covered by a sensing membrane and a biointerface membrane (not shown), which are described in more detail below.

[0094] The body 20 is preferably formed from epoxy molded around the sensor electronics, however the body can be formed from a variety of materials, including metals, ceramics, plastics, or composites thereof. U.S. Patent Application No. 10/646,333, filed August 22, suitable configurations suitable for the body 20.

[0095] In one embodiment, the sensing region 22 comprises three electrodes including a platinum working electrode, a platinum counter electrode, and a silver/silver chloride reference electrode, for example. However a variety of electrode

materials and configurations can be used with the implantable glucose sensor of the preferred embodiments. The top ends of the electrodes are in contact with an electrolyte phase (not shown), which is a free-flowing fluid phase disposed between the sensing membrane and the electrodes. In one embodiment, the counter electrode is provided to balance the current generated by the species being measured at the working electrode. In the case of a glucose oxidase based glucose sensor, the species being measured at the working electrode is H_2O_2. Glucose oxidase catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate according to the following reaction:

$$\text{Glucose} + O_2 \rightarrow \text{Gluconate} + H_2O_2$$

[0096] The change in H_2O_2 can be monitored to determine glucose concentration because for each glucose molecule metabolized, there is a proportional change in the product H_2O_2. Oxidation of H_2O_2 by the working electrode is balanced by reduction of ambient oxygen, enzyme generated H_2O_2, or other reducible species at the counter electrode. The H_2O_2 produced from the glucose oxidase reaction further reacts at the surface of working electrode and produces two protons ($2H^+$), two electrons ($2e^-$), and one oxygen molecule (O_2).

[0097] In one embodiment, a potentiostat (Fig. 3) is employed to monitor the electrochemical reaction at the electroactive surface(s). The potentiostat applies a constant potential to the working and reference electrodes to determine a current value. The current that is produced at the working electrode (and flows through the circuitry to the counter electrode) is substantially proportional to the amount of H_2O_2 that diffuses to the working electrode. Accordingly, a raw signal can be produced that is representative of the concentration of glucose in the user's body, and therefore can be utilized to estimate a meaningful glucose value.

[0098] In some embodiments, the sensing membrane includes an enzyme, for example, glucose oxidase, and covers the electrolyte phase. In one embodiment, the sensing membrane generally includes a resistance domain most distal from the electrochemically reactive surfaces, an enzyme domain less distal from the electrochemically reactive surfaces than the resistance domain, and an electrolyte domain adjacent to the electrochemically reactive surfaces. However, it is understood that a sensing membrane modified for other devices, for example, by including fewer or additional domains, is within the scope of the preferred embodiments. U.S. Publication No. 2003/0032874, entitled, "SENSOR HEAD FOR USE WITH IMPLANTABLE DEVICES," describes membranes that can be used in some embodiments of the sensing membrane. blocks some interfering species; such as described in the above-cited co-pending patent application. U.S. Patent Application 10/695,636, entitled, "SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE" also describes membranes that can be used for the sensing membrane of the preferred embodiments.

[0099] Preferably, the biointerface membrane supports tissue ingrowth, serves to interfere with the formation of a barrier cell layer, and protects the sensitive regions of the device from host inflammatory response. In one embodiment, the biointerface membrane generally includes a cell disruptive domain most distal from the electrochemically reactive surfaces and a cell impermeable domain less distal from the electrochemically reactive surfaces than the cell disruptive domain. The cell disruptive domain is preferably designed to support tissue ingrowth, disrupt contractile forces typically found in a foreign body response, encourage vascularity within the membrane, and disrupt the formation of a barrier cell layer. The cell impermeable domain is preferably resistant to cellular attachment, impermeable to cells, and composed of a biostable material. U.S. Patent No. 6,702,857, entitled, "MEMBRANE FOR USE WITH IMPLANTABLE DEVICES," U.S. Patent Application 10/647,065, entitled, "POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES," and U.S. Patent Application entitled, "BIOINTERFACE WITH INTEGRATED MACRO- AND MICRO-ARCHITECTURE," filed February 9, 2005, describe biointerface membranes that can be used in conjunction with the preferred embodiments. The preferred embodiments can be used with a short term (for example, 1 to 7 day sensor), in which case a biointerface membrane may not be required. The biointerface membranes described herein provide a continuous glucose sensor that has a useable life of greater than about one week, greater than about one month, greater than about three months, or greater than about one year, herein after referred to as "long-term."

[0100] In some embodiments, the domains of the biointerface and sensing membranes are formed from materials such as silicone, polytetrafluoroethylene, polyethylene-co-tetrafluoroethylene, polyolefin, polyester, polycarbonate, biostable polytetrafluoroethylene, homopolymers, copolymers, terpolymers of polyurethanes, polypropylene (PP), polyvinylchloride (PVC), polyvinylidene fluoride (PVDF), polybutylene terephthalate (PBT), polymethylmethacrylate (PMMA), polyether ether ketone (PEEK), polyurethanes, cellulosic polymers, polysulfones and block copolymers thereof including, for example, di-block, tri-block, alternating, random and graft copolymers.

[0101] Fig. 3 is a block diagram that illustrates the electronics associated with a continuous glucose sensor 12 in one embodiment. In this embodiment, a potentiostat 24 is shown, which is operably connected to electrodes (Fig. 2) to obtain a current value, and includes a resistor (not shown) that translates the current into voltage. An A/D converter 26 digitizes the analog signal to the current measured by the potentiostat 24.

[0102] A microprocessor 28 is the central control unit that houses ROM 30 and RAM 32, and controls the processing of the sensor electronics. Certain alternative embodiments can utilize a computer system other than a microprocessor to process data as described herein. In some alternative embodiments, an application-specific integrated circuit (ASIC)

can be used for some or all the sensor's central processing as is appreciated by one skilled in the art. The ROM 30 provides semi-permanent storage of data, for example, storing data such as sensor identifier (ID) and programming to process data streams (for example, programming for data smoothing and/or replacement of signal artifacts such as described in U.S. Patent Application No. 10/646,333 entitled, "SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM," filed August 22, 2003). The RAM 32 can be used for the system's cache memory, for example for temporarily storing recent sensor data. In some alternative embodiments, memory storage components comparable to ROM 30 and RAM 32 can be used instead of or in addition to the preferred hardware, such as dynamic RAM, static-RAM, non-static RAM, EEPROM, rewritable ROMs, flash memory, or the like.

[0103] A battery 34 is operably connected to the microprocessor 28 and provides the necessary power for the sensor 12. In one embodiment, the battery is a Lithium Manganese Dioxide battery, however any appropriately sized and powered battery can be used (for example, AAA, Nickel-cadmium, Zinc-carbon, Alkaline, Lithium, Nickel-metal hydride, Lithium-ion, Zinc-air, Zinc-mercury oxide, Silver-zinc, and/or hermetically-sealed). In some embodiments the battery is rechargeable. In some embodiments, a plurality of batteries can be used to power the system. In yet other embodiments, the receiver can be transcutaneously powered via an inductive coupling, for example. A Quartz Crystal 36 is operably connected to the microprocessor 28 and maintains system time for the computer system as a whole.

[0104] An RF Transceiver 38 is operably connected to the microprocessor 28 and transmits the sensor data from the sensor 12 to a receiver within a wireless transmission 40 via antenna 42. Although an RF transceiver is shown here, some other embodiments can include a wired rather than wireless connection to the receiver. A second quartz crystal 44 provides the system time for synchronizing the data transmissions from the RF transceiver. The transceiver 38 can be substituted with a transmitter in other embodiments. In some alternative embodiments other mechanisms such as optical, infrared radiation (IR), ultrasonic, or the like can be used to transmit and/or receive data.

[0105] In one alternative embodiment, the continuous glucose sensor comprises a transcutaneous sensor such as described in U.S. Patent 6,565,509 to Say et al. In another alternative embodiment, the continuous glucose sensor comprises a subcutaneous sensor such as described In another alternative embodiment, the continuous glucose sensor comprises a refillable subcutaneous sensor such as described with reference to U.S. Patent 6,512,939 to Colvin et al. In another alternative embodiment, the continuous glucose sensor comprises an intravascular sensor such as described with reference to U.S. Patent 6,477,395 to Schulman et al. In another alternative embodiment, the continuous glucose sensor comprises an intravascular sensor such as described with reference to U.S. Patent 6,424,847 to Mastrototaro et al. In general, the disclosed embodiments are applicable to a variety of continuous glucose sensor configurations.

[0106] In various embodiments, the continuous glucose sensor is configured to operate over a period of hours, days, weeks, or months. In one embodiment, the sensor is configured to operate for at least one day, such as one day, two days, three days, etc. In one embodiment, the sensor is configured to operate for at least three days. In one embodiment, the sensor is configured to operate for at least one week, such as one week, two weeks, three weeks, etc. In one embodiment, the sensor is configured to operate for at least one month, such as one month, two months, three months, etc.

Receiver

[0107] The preferred embodiments provide an integrated system, which includes a receiver 14 that receives and processes the raw data stream from the continuous glucose sensor 12. The receiver can perform all or some of the following operations: a calibration, converting sensor data, updating the calibration, evaluating received reference and sensor data, evaluating the calibration for the analyte sensor, validating received reference and sensor data, displaying a meaningful glucose value to a user, calculating therapy recommendations, validating recommended therapy, adaptive programming for learning individual metabolic patterns, and prediction of glucose values, for example. Some complementary systems and methods associated with the receiver are described in more detail with reference to co-pending U.S. Patent Application 10/633,367, entitled, "SYSTEM AND METHODS FOR PROCESSING ANALITTE SENSOR DATA." Figs. 9 to 11 describe some processes that can be programmed into the receiver. Additionally, the receiver 14 of the preferred embodiments works together with the other components of the system (for example, the medicament delivery device 16 and the single point glucose monitor 18) to provide enhanced functionality, convenience, and safety, such as described in more detail herein. Figs. 4 to 7 are illustrates of a few exemplary integrated systems of the preferred embodiments, each of which include the receiver, such as described in more detail herein.

[0108] In some embodiments, the receiver 14 is a PDA- or pager-sized housing 46, for example, and comprises a user interface 48 that has a plurality of buttons 50 and a liquid crystal display (LCD) screen, which can include a backlight. In some embodiments, the receiver can take other forms, for example a computer, server, or other such device capable of receiving and include a keyboard, a speaker, and a vibrator such as described with reference to Fig. 8. The receiver 46 comprises systems (for example, electronics) necessary to receive, process, and display sensor data from the glucose sensor 12, such as described in more detail with reference to Fig. 8. The receiver 14 processes data from the continuous glucose sensor 12 and additionally processes data associated with at least one of the medicament delivery device 16, single point glucose meter 16, and user 8.

[0109] In some embodiments, the receiver 14 is integrally formed with at least one of the medicament delivery device 16, and single point glucose monitor 18. In some embodiments, the receiver 14, medicament delivery device 16 and/or single point glucose monitor 18 are detachably connected, so that one or more of the components can be individually detached and attached at the user's convenience. In some embodiments, the receiver 14, medicament delivery device 16, and/or single point glucose monitor 18 are separate from, detachably connectable to, or integral with each other; and one or more of the components are operably connected through a wired or wireless connection, allowing data transfer and thus integration between the components. In some embodiments, one or more of the components are operably linked as described above, while another one or more components (for example, the syringe or patch) are provided as a physical part of the system for convenience to the user and as a reminder to enter data for manual integration of the component with the system. Some exemplary embodiments are described with reference to Figs. 4 to 7, however, each of the components of the integrated system can be manually, semi-automatically, or automatically integrated with each other, and each component can be in physical and/or data communication with another component, which can include wireless connection, wired connection (for example, via cables or electrical contacts), or the like.

Medicament Delivery Device

[0110] The preferred embodiments provide an integrated system 10, which includes a medicament delivery device 16 for administering a medicament to the patient 8. The integrated medicament delivery device can be designed for bolus injection, continuous injection, inhalation, transdermal absorption, other method for administering medicament, or any combinations thereof. The term medicament includes any substance used in therapy for a patient using the system 10, for example, insulin, glucacon, or derivatives thereof. Published International Application WO 02/43566 describes glucose, glucagon, and vitamins A, C, or D that can be used with the preferred embodiments. U.S. Patents 6,051,551 and 6,024,090 describe types of insulin suitable for inhalation that can be used with the preferred embodiments. Patents U.S. 5,234,906, U.S. 6,319,893, and EP 760677 describe various derivatives of glucagon that can be used with the preferred embodiments. U.S. Patent 6,653,332 describes a combination therapy that can be used with the preferred embodiments. U.S. Patent 6,471,689 and WO 81/01794 describe insulin useful describes a method of providing more than one type of insulin that can be used with the preferred embodiments.

Manual Integration

[0111] In some embodiments, the medicament delivery device 16 is a manual delivery device, for example a syringe, inhaler, transdermal patch, cell transplantation device, and/or manual pump for manual integration with the receiver. Manual integration includes medicament delivery devices wherein a user (for example, patient or doctor) manually selects the amount, type, and/or time of delivery. In some embodiments, the medicament delivery device 16 is any syringe suitable for injecting a medicament, as is appreciated by one skilled in the art. One example of a syringe suitable for the medicament delivery device of the preferred embodiments is described in U.S. Patent 5,137,511.

[0112] Figs. 4A and 4B are perspective views of an integrated system 10 in one embodiment, wherein a receiver 14 is integrated with a medicament delivery device 16 in the form of a manual syringe 54, and optionally includes a single point glucose monitor 18, which are described in more detail elsewhere herein. The receiver 14 receives, processes, and displays data from the continuous glucose monitor 12, such as described in more detail above, and can also receive, process, and display data manually entered by the user. In some embodiments, the receiver includes algorithms that use parameters provided by the continuous glucose sensor, such as glucose concentration, rate-of-change of the glucose concentration, and acceleration of the glucose concentration to more particularly determine the type, amount, and time of medicament administration. The medicament delivery device 16 is in the form of a syringe 54, which can comprise any known syringe configuration, such as described in more detail above. In some embodiments, the syringe 54 includes a housing, which is designed to hold a syringe as well as a plurality of types and amounts of medicament, for example fast-acting insulin, slow-acting insulin, and glucagon. In some embodiments, the syringe is detachably connectable to the receiver 14, and the receiver 14 provides and receives information to and from the patient associated with the time, type, and amount of medicament administered. In some embodiments, the syringe is stored in a holder that is integral with or detachably connected to the receiver 14. In some embodiments, the syringe 54 can be detachable connected directly to the receiver, provided in a kit with the receiver, or other configuration, which provides easy association between the syringe and the receiver.

[0113] Referring now to the integration between the syringe and the receiver, the receiver can be programmed with information about the time, amount, and types of medicament that can be administered with the syringe, for example. In some embodiments during set-up of the system, the patient and/or doctor manually enters information about the amounts and types of medicament available via the syringe of the integrated system. In some alternative embodiments, select appropriate information from menus on the screen, for example, to provide easy and accurate data entry. Thus, by knowing the available medicaments, the receiver can be programmed to customize the patient's therapy recommen-

dations considering available types and amounts of medicaments in combination with concentration, rate-of-change, and/or acceleration of the patient's glucose. While not wishing to be bound by theory, it is believed that by storing available medicament therapies, the receiver is able to customize medicament calculations and recommend appropriate therapy based glucose on trend information and the preferred types and the amounts of medicament available to the patient.

[0114] Subsequently in some embodiments, once the patient has administered a medicament (including via the syringe and or by other means), the amount, type, and/or time of medicament administration are input into the receiver by the patient. Similarly, the receiver can be programmed with standard medicaments and dosages for easy selection by the patient (for example, menus on the user interface). This information can be used by the receiver to increase the intelligence of the algorithms used in determining the glucose trends and patterns that can be useful in predicting and analyzing present, past, and future glucose trends, and in providing therapy recommendations, which are described in more detail below. Additionally, by continuously monitoring the glucose concentration over time, the receiver provides valuable information about how a patient responds to a particular medicament, which information can be used by a doctor, patient, or by the algorithms within the receiver, to determine patterns and provide more personalized therapy recommendations. In other words, in some embodiments, the receiver includes programming that learns the patterns (for example, an individual's metabolic response to certain medicament deliveries and patient behavior) and to determine an optimum time, amount, and type of medicament to delivery in a variety of conditions (e.g., glucose concentration, rate-of-change, and acceleration). While not wishing to be bound by theory, it is believed that by continuously monitoring an individual's response to various medicaments, the patient's glucose levels can be more proactively treated, keeping the diabetic patient within safe glucose ranges substantially all the time.

[0115] In some embodiments, the receiver includes programming to predict glucose trends, such as described in U.S. Patent Application 11/007,920, entitled, "SIGNAL PROCESSING FOR CONTINUOUS ANALYTE SENSORS." In some embodiments, the predictive algorithms consider the amount, type, and time of medicament delivery in predicting glucose values. For example, a predictive algorithm that predicts a glucose value or trend for the upcoming 15 to 20 minutes uses a mathematical algorithm (for example, regression, smoothing, or the like) such as described in the above-cited patent application 11/007,920 to project a glucose value. However outside influences, including medicament delivery may cause this projection to be inaccurate. delivery information received from the delivery device 14, in addition to other mathematical equations, to more accurately predict glucose values in the future.

[0116] In some alternative embodiments, the medicament delivery device 16 includes one or more transdermal patches 58 suitable for administering medicaments as is appreciated by one skilled in the art. WO 02/43566 describes one such transdermal patch, which can be used in the preferred embodiments. Although the above-cited reference and description associated with the Figs. 5A to 5C describe a medicament (for example, glucagon) useful for treating hypoglycemia, it is understood that transdermal patches that release a medicament (for example, insulin) useful for treating hyperglycemia are also contemplated within the scope of the preferred embodiments.

[0117] Figs. 5A to 5C are perspective views of an integrated system 10 in one embodiment, wherein a receiver 14 is integrated with a medicament delivery device 16 in the form of one or more transdermal patches 58 housed within a holder 56, and optionally includes a single point glucose monitor 18, which are described in more detail elsewhere herein. The receiver 14 receives, processes, and displays data from the continuous glucose monitor 12, such as described in more detail above. The medicament delivery device 16 is in the form of one or more transdermal patches 58 held in a holder 56, which can comprise any known patch configuration.

[0118] The integration of the patches 58 with the receiver 14 includes similar functionality and provides similar advantages as described with reference to other manual integrations including manual medicament delivery devices (for example, syringe and inhaler). However, a unique advantage can be achieved in the integration of a continuous glucose sensor with a glucagon-type patch. Namely, a continuous glucose sensor, such as described in the preferred embodiments, provides more than single point glucose readings. In fact, because the continuous glucose sensor 12 knows the concentration, rate-of-change, acceleration, the amount of insulin administered (in some embodiments), and/or individual patterns associated with a patient's glucose trends (learned over time as described in more detail elsewhere herein), the use of the glucagon patch can be iteratively optimized (inputting its usage into the receiver and monitoring the individual's metabolic response) to proactively preempt hypoglycemic events and maintain a more controlled range of glucose values. This can be particularly advantageous for nighttime hypoglycemia by enabling the diabetic patient (and his/her caretakers) to improve overall nighttime diabetic health. While not wishing to be bound by theory, the integration of the continuous glucose sensor and transdermal glucagon-type patch can provide diabetic patients with a long-term solution to reduce or avoid hypoglycemic events.

[0119] In some embodiments, the holder 58 is detachably connectable to the receiver 14 (for example on the side opposite the LCD), which enables convenient availability of the patch to the patient when the receiver indicates that a medicament (for example, glucose or glucagon) is the illustrations of Figs. 5A to 5C, other medicaments (for example, insulin pen, insulin pump, such as described with reference to Figs. 6 and 7) can be integrated into the system in combination with the medicament patch illustrated herein. While not wishing to be bound by theory, it is believed that by combining medicaments that aid the diabetic patient in different ways (for example, medicaments for treating hyper-

and hypo-glycemic events, or, fast-acting and slow-acting medicaments), a simplified comprehensive solution for treating diabetes can be provided.

[0120] Manual Integration of delivery devices with the continuous glucose sensor 12 of the preferred embodiments can additionally be advantageous because the continuous device of the preferred embodiments is able to track glucose levels long-term (for example weeks to months) and adaptively improve therapy decisions based on the patients response over time.

[0121] In some alternative embodiments, the medicament delivery device 16 includes an inhaler or spray device suitable for administering a medicament into the circulatory system, as is appreciated by one skilled in the art. Some examples of inhalers suitable for use with the preferred embodiments include U.S. Patents 6,167,880, 6,451,551, 6,024,090. In some embodiments, the inhaler or spray device is considered a manual medicament delivery device, such as described with reference to Figs. 4 and 5, wherein the inhaler or spray is manually administered by a patient, and wherein the patient manually enters data into the continuous receiver about the time, amount, and types of therapy. However, it is also possible that the inhaler or spray device used for administering the medicament can also comprise a microprocessor and operable connection to the receiver (for example, RF), such that data is sent and received between the receiver and inhaler or spray device, making it a semi-automated integration, which is described in more detail with reference to the integrated insulin pen below, for examples.

[0122] In some embodiments, the inhaler or spray device is integrally housed within, detachably connected to, or otherwise physically associated with (for example, in a kit) to the receiver. The functionality and advantages for the integrated inhaler or spray device are similar to those described with reference to the syringe and/or patch integration, above. The inhaler or spray device can be provided in combination with any other of the medicament delivery devices of the preferred embodiments, for example, a fast-acting insulin inhaler and a slow acting insulin pump can be advantageously integrated into the system of the preferred embodiments and utilized at the appropriate time as is appreciated by one skilled in the art. In some embodiments, wherein the inhaler or spray device includes a semi-automated integration with the receiver, the inhaler or spray device can by physically integrated with receiver such as described above and also operably connected to the receiver, for example via a wired (for example, via electrical contacts) or wireless (for example, via RF) connection.

implanted such as described in U.S. Patent 6,283,944. In this alternative embodiment, the patient-controlled implantable pump allows the patient to press on the device (through the skin) to administer a bolus injection of a medicament when needed. It is believed that providing glucagon or other medicament for treating hypoglycemia within this device can provide the ease and convenience that can be easily released by the patient and/or his or her caretaker when the continuous glucose sensor indicates severe hypoglycemia, for example. In some alternative embodiments, the manual implantable pump is filled with insulin, or other medicament for treating hyperglycemia. In either embodiment, the manual pump or continuous glucose sensor can benefit from manual integrations described in more detail above.

[0123] In another alternative embodiment, a cell transplantation device, such as described in U.S. Patents 6,015,572, 5,964,745, and 6,083,523, is manually integrated with the continuous sensor of the preferred embodiments. In this alternative embodiment, a patient would be implanted with beta islet cells, which provide insulin secretion responsive to glucose levels in the body. The receiver associated with the implantable glucose sensor can be programmed with information about the cell transplantation (for example, time, amount, type, etc). In this way, the long-term continuous glucose sensor can be used to monitor the body's response to the beta islet cells. This can be particularly advantageous when a patient has been using the continuous glucose sensor for some amount of time prior to the cell transplantation, and the change in the individual's metabolic patterns associated with the transplantation of the cells can be monitored and quantified. Because of the long-term continuous nature of the glucose sensor of the preferred embodiments, the long-term continuous effects of the cell transplantation can be consistently and reliably monitored. This integration can be advantageous to monitor any person's response to cell transplantation before and/or after the implantation of the cells, which can be helpful in providing data to justify the implantation of islet cells in the treatment of diabetes.

[0124] Any of the manual medicament delivery devices can be provided with an RF ID tag or other communication-type device, which allows semi-automated integration with that manual delivery device, such as described in more detail below.

Semi-automated Integration

[0125] Semi-automated integration of medicament delivery devices 16 in the preferred embodiments includes any integration wherein an operable connection between the integrated components aids the user (for example, patient or doctor) in selecting, inputting, or calculating the amount, type, or time of medicament delivery of glucose values, for example, by transmitting data to another component and thereby reducing the amount of user input required. In the preferred embodiments, semi-automated can also refer to a fully automated device (for example, one that does not require user interaction), wherein the fully automated device requires a validation or other embodiments, the semi-automated medicament delivery device is an inhaler or spray device, a pen or jet-type injector, or a transdermal or

implantable pump.

[0126] Figs. 6A and 6B are perspective views of an integrated system 10 in one embodiment, wherein a receiver 14 is integrated with a medicament delivery device 16 in the form of a pen or jet-type injector, hereinafter referred to as a pen 60, and optionally includes a single point glucose monitor 18, which are described in more detail elsewhere herein. The receiver 14 receives, processes, and displays data from the continuous glucose monitor 12, such as described in more detail above. The medicament delivery pen 60 of the preferred embodiments, includes any pen-type injector, such as is appreciated by one skilled in the art. A few examples of medicament pens that can be used with the preferred embodiments, include U.S. Patents 5,226,895, 4,865,591, 6,192,891, and 5,536,249.

[0127] Fig. 6A is a perspective view of an integrated system 10 in embodiment. The integrated system 10 is shown in an attached state, wherein the various elements are held by a mechanical means, as is appreciated by one skilled in the art. The components 14, 16, and 18(optional) are also in operable connection with each other, which can include a wired or wireless connection. In some embodiments, the components include electrical contacts that operably connect the components together when in the attached state. In some embodiments, the components are operably connected via wireless connection (for example, RF), and wherein the components may or may not be detachably connectable to each other. Fig. 6B shows the components in an unattached state, which can be useful when the patient would like to carry minimal components and/or when the components are integrated via a wireless connection, for example.

[0128] Medicament delivery pen 60 includes at least a microprocessor and a wired or wireless connection to the receiver 14, which are described in more detail with reference to Fig. 8. In some embodiments, the pen 60 includes programming that receives instructions sent from the receiver 14 regarding type and amount of medicament to administer. In some embodiments, wherein the pen includes more than one type of medicament, the receiver provides the necessary instructions to determine which type or types of medicament to administer, and can provide instructions necessary for mixing the one or more medicaments. In some embodiments, the receiver provides the glucose trend information (for example, concentration, rate-of-change, acceleration, or other user input information) and pen 60 includes programming necessary to determine appropriate medicament delivery.

[0129] Subsequently, the pen 60 includes programming to send information regarding the amount, type, and time of medicament delivery to the receiver 14 for processing. The receiver 14 can use this information received from the pen 60, in combination with the continuous glucose data obtained from the sensor, to monitor and determine the patient's glucose patterns to measure and amount of medicament delivery can be useful in adjusting or optimizing the patient's therapy. Individual metabolic profiles (for example, insulin sensitivity) are variable from patient to patient. While not wishing to be bound by theory, it is believed that once the receiver has learned (for example, monitored and determined) the individual's metabolic patterns, including glucose trends and associated medicament deliveries, the receiver can be programmed to adjust and optimize the therapy recommendations for the patient's individual physiology to maintain their glucose levels within a desired target range. In alternative embodiments, the pen 60 can be manually integrated with the receiver.

[0130] In some embodiments, the receiver includes algorithms that use parameters provided by the continuous glucose sensor, such as glucose concentration, rate-of-change of the glucose concentration, and acceleration of the glucose concentration to more particularly determine the type, amount, and time of medicament administration. In fact, all of the functionality of the above-described manual and semi-automated integrated systems, including therapy recommendations, adaptive programming for learning individual metabolic patterns, and prediction of glucose values, can be applied to the semi-automated integrated system 10, such as described herein. However, the semi- automated integrated sensing and delivery system additionally provides convenience by automation (for example, data transfer through operable connection) and reduced opportunity for human error than may be experienced with the manual integration.

[0131] In some alternative embodiments, the semi-automated integration provides programming that requires at least one of the receiver 14, single point glucose monitor 18, and medicament delivery device 16 to be validated or confirmed by another of the components to provide a fail safe accuracy check; in these embodiments, the validation includes algorithms programmed into any one or more of the components. In some alternative embodiments, the semi-automated integration provides programming that requires at least one of the receiver 14 and medicament delivery device 16 to be validated or confirmed by an a human (for example, confirm the amount and/or type of medicament). In these embodiments, validation provides a means by which the receiver can be used adjunctively, when the patient or doctor would like to have more control over the patient's therapy decisions, for example. See Figs. 9 to 11 for processes that can be implemented herein.

[0132] Although the above description of semi-automated medicament delivery is mostly directed to an integrated delivery pen, the same or similar integration can be accomplished between a semi-automated inhaler or spray device, and/or a semi-automated transdermal or implantable pump device. Additionally, any combination of the above semi-automated medicament delivery devices can be combined with other manual and/or automated medicament delivery device within the scope of the preferred embodiments as is appreciated by one skilled in the art.

[0133] Automated integration medicament delivery devices 16 in the preferred embodiments are any delivery devices wherein an operable connection between the integrated components provides for full control of the system without

required user interaction. Transdermal and implantable pumps are examples of medicament delivery devices that can be used with the preferred embodiments of the integrated system 10 to provide automated control of the medicament delivery device 16 and continuous glucose sensor 12. Some examples of medicament pumps that can be used with the preferred embodiments include, Patents U.S. 6,471,689, WO 81/01794, and EP 1281351.

[0134] Figs. 7A to 7C are perspective views of an integrated system in one embodiment, wherein a sensor and delivery pump, which are implanted subcutaneously or transdermally inserted into the patient, are operably connected to an integrated receiver, and optionally include a single point glucose monitor. Fig. 7A is a perspective view of a patient 8, in which is implanted or transdermally inserted a sensor 12 and a pump 70. Figs. 7B and 7C are perspective views of the integrated receiver and optional single point glucose monitor in attached and unattached states. The pump 70 can be of any configuration known in the art, for example, such as cited above.

[0135] The receiver 14 receives, processes, and displays data associated with the continuous glucose monitor 12, data associated with the pump 70, and data manually entered by the patient 8. In some embodiments, the receiver includes algorithms that use parameters provided by the continuous glucose sensor, such as glucose concentration, rate-of-change of the glucose concentration, and acceleration of the glucose concentration to determine the type, amount, and time of medicament administration. In fact, all of the functionality of the above-described manual and semi-automated integrated systems, including therapy recommendations, confirmation or validation of medicament delivery, adaptive programming for learning individual metabolic patterns, and prediction of glucose values, can be applied to the fully automated integrated system 10, such as described herein with reference to Figs. 7A to 7C. However, the fully automated sensing and delivery system can run with or without user interaction. Published Patent Application US 2003/0028089 provides some systems and methods for providing control of insulin, which can be used with the preferred embodiments.

[0136] In some embodiments of the automated integrated system 10, a fail-safe mode is provided, wherein the system is programmed with conditions whereby when anomalies or potentially clinically risky situations arise, for example when a reference glucose value (for example, from an SMBG) indicates a discrepancy from the continuous sensor that could cause risk to the patient if incorrect therapy is administered. Another example of a situation that can benefit from a validation includes when a glucose values are showing a trend in a first direction that shows behavior within a few minutes to an hour, for example. In such situations, the automated system can be programmed to revert to a semi-automated system requiring user validation or other user interaction to validate the therapy in view of the situation.

[0137] In the illustrated embodiment, only one receiver 14 is shown, which houses the electronics for both the medicament delivery pump 70 and the continuous sensor 12. Although it is possible to house the electronics in two different receiver housings, providing one integrated housing 14 increases patient convenience and minimizes confusion or errors. In some embodiments, the sensor receiver electronics and pump electronics are separate, but integrated. In some alternative embodiments, the sensor and pump share the same electronics.

[0138] Additionally, the integrated receiver for the sensor and pump, can be further integrated with any combination with the above-described integrated medicament delivery devices, including syringe, patch, inhaler, and pen, as is appreciated by one skilled in the art.

Single Point Glucose Monitor

[0139] In the illustrated embodiments (Figs. 4 to 7), the single point glucose monitor includes a meter for measuring glucose within a biological sample including a sensing region that has a sensing membrane impregnated with an enzyme, similar to the sensing membrane described with reference to U.S. Patents 4,994,167 and 4,757,022. However, in alternative embodiments, the single point glucose monitor can use other measurement techniques such as optical, for example. The meter is optional in that a separate meter can be used and the glucose data downloaded or input by a user into the receiver. However the illustrated embodiments show an integrated system that exploits the advantages associated with integration of the single point glucose monitor with the receiver 14 and delivery device 16.

[0140] Figs. 4 to 7 are perspective views of integrated receivers including a single point glucose monitor. The integrated single point glucose monitor can be integral with, detachably connected to, and/or operably connected (wired or wireless) to the receiver 14 and medicament delivery device 16. The single point glucose monitor 18 integrates rapid and accurate measurement of the amount of glucose in a biological fluid and its associated processing with the calibration, validation, other processes associated with the continuous receiver 14, such as described in more detail with reference to U.S. Patent Application 10/991,966, entitled "INTEGRATED RECEIVER

FOR CONTINUOUS ANALYTE SENSOR."

[0141] In the illustrated embodiments, the single point glucose monitor 18, such as described in the above-cited patent application 10/991,966, includes a body 62 that houses a sensing region 64, which includes a sensing membrane located within a port. A shuttle mechanism 66 can be provided that preferably feeds a single-use disposable bioprotective film that can be placed over the sensing region 64 to provide protection from contamination. The sensing region which is a

free-flowing fluid phase disposed between the sensing membrane and the electrodes. The sensing region measures glucose in the biological sample in a manner such as described in more detail above, with reference the continuous glucose sensor and/or U.S. Patents 4,994,167 and 4,757,022. The similarity of the measurement technologies used for the continuous glucose sensor and the single point glucose sensor provides an internal control that creates increased reliability by nature of consistency and decreased error potential that can otherwise be increased due to combining dissimilar measurement techniques. Additionally, the disclosed membrane system is known to provide longevity, repeatability, and cost effectiveness, for example as compared to single use strips, or the like. However, other single point glucose monitors can be used with the preferred embodiments.

[0142] In one alternative embodiment, the single point glucose monitor comprises an integrated lancing and measurement device such as described in U.S. Patent 6,607,658 to Heller et al. In another alternative embodiment, the single point glucose monitor comprises a near infrared device such as described in U.S. Patent 5,068,536 to Rosenthal et al. In another alternative embodiment, the single point glucose monitor comprises a reflectance reading apparatus such as described in U.S. Patent 5,426,032 to Phillips et al. In another alternative embodiment, the single point glucose monitor comprises a spectroscopic transflectance device such as described in U.S. Patent 6,309,884 to Cooper et al.

[0143] In some embodiments, the single point glucose meter further comprises a user interface that includes a display 72 and a button 74; however, some embodiments utilize the display 48 and buttons 50 of the receiver 14 rather than providing a separate user interface for the monitor 18. In some embodiments the single point glucose monitor measured glucose concentration, prompts, and/or messages can be displayed on the user interface 48 or 72 to guide the user through the calibration and sample measurement procedures, or the like. In addition, prompts can be displayed to inform the user about necessary maintenance procedures, such as "Replace Sensor" or "Replace Battery." The button 74 preferably initiates the operation and calibration sequences. The button can be used to refresh, calibrate, or otherwise interface with the single point glucose monitor 18 as is appreciated by one skilled in the art.

Integrated Electronics

[0144] Fig. 8 is a block diagram that illustrates integrated system electronics in one embodiment. One embodiment is described wherein the microprocessor within the receiver performs much of the processing, however it is understood that all or some of the programming and processing described herein can be accomplished within continuous glucose sensor, receiver, single point glucose monitor, and/or delivery device, or any combination thereof. Similarly, displays, components of the integrated delivery device.

[0145] A quartz crystal 76 is operably connected to an RF transceiver 78 that together function to receive and synchronize data streams via an antenna 80 (for example, transmission 40 from the RF transceiver 44 shown in Fig. 3). Once received, a microprocessor 82 processes the signals, such as described below.

[0146] The microprocessor 82 is the central control unit that provides the processing for the receiver, such as storing data, analyzing continuous glucose sensor data stream, analyzing single point glucose values, accuracy checking, checking clinical acceptability, calibrating sensor data, downloading data, recommending therapy instructions, calculating medicament delivery amount, type and time, learning individual metabolic patterns, and controlling the user interface by providing prompts, messages, warnings and alarms, or the like. The ROM 84 is operably connected to the microprocessor 82 and provides semi-permanent storage of data, storing data such as receiver ID and programming to process data streams (for example, programming for performing calibration and other algorithms described elsewhere herein). RAM 88 is used for the system's cache memory and is helpful in data processing. For example, the RAM 88 stores information from the continuous glucose sensor, delivery device, and/or single point glucose monitor for later recall by the user or a doctor; a user or doctor can transcribe the stored information at a later time to determine compliance with the medical regimen or evaluation of glucose response to medication administration (for example, this can be accomplished by downloading the information through the pc com port 90). In addition, the RAM 88 can also store updated program instructions and/or patient specific information. Figs. 9 and 10 describe more detail about programming that is preferably processed by the microprocessor 82. In some alternative embodiments, memory storage components comparable to ROM and RAM can be used instead of or in addition to the preferred hardware, such as SRAM, EEPROM, dynamic RAM, non-static RAM, rewritable ROMs, flash memory, or the like.

[0147] In some embodiments, the microprocessor 82 monitors the continuous glucose sensor data stream 40 to determine a preferable time for capturing glucose concentration values using the single point glucose monitor electronics 116 for calibration of the continuous sensor data stream. For example, when sensor glucose data (for example, observed from the data stream) changes too rapidly, a single point glucose monitor reading may not be sufficiently reliable for calibration during unstable glucose changes in the host; in contrast, when sensor glucose data are relatively stable (for example, relatively low rate of change), a single point glucose monitor reading can be taken for a reliable calibration. In some additional embodiments, the microprocessor can prompt the user via the user interface to obtain a single point glucose value for calibration at predetermined intervals. In some additional embodiments, the user interface can prompt the user to meals, exercise, large excursions in glucose levels, faulty or interrupted data readings, or the like. In some

embodiments, certain acceptability parameters can be set for reference values received from the single point glucose monitor. For example, in one embodiment, the receiver only accepts reference glucose data between about 40 and about 400 mg/dL.

[0148] In some embodiments, the microprocessor 82 monitors the continuous glucose sensor data stream to determine a preferable time for medicament delivery, including type, amount, and time. In some embodiments, the microprocessor is programmed to detect impending clinical risk and can request data input, a reference glucose value from the single point glucose monitor, or the like, in order to confirm a therapy recommendation. In some embodiments, the microprocessor is programmed to process continuous glucose data and medicament therapies to adaptive adjust to an individual's metabolic patterns. In some embodiments, the microprocessor is programmed to project glucose trends based on data from the integrated system (for example, medicament delivery information, user input, or the like). In some embodiments, the microprocessor is programmed to calibrate the continuous glucose sensor based on the integrated single point glucose monitor. Numerous other programming can be incorporated into the microprocessor, as is appreciated by one skilled in the art, as is described in cited patents and patent applications here, and as is described with reference to flowcharts of Figs. 9 to 11.

[0149] One advantage of integrated system of the preferred embodiments can be seen in the time stamp of the sensor glucose data, medicament delivery data, and reference glucose data. Namely, typical implementations of the continuous glucose sensor 12, wherein the medicament delivery 16 and/or single point glucose monitor 18 is not integral with the receiver 14, the reference glucose data or medicament delivery data can be obtained at a time that is different from the time that the data is input into the receiver 14. Thus, the user may not accurately input the "time stamp" of the delivery or (for example, the time or obtaining reference glucose value or administering the medicament) at the time of reference data input into the receiver. Therefore, the accuracy of the calibration of the continuous sensor, prediction of glucose values, therapy recommendations, and other processing is subject to human error (for example, due to inconsistencies in entering the actual time of the single point glucose test). In contrast, the preferred embodiments of the integrated system advantageously do no suffer from this potential inaccuracy when the time stamp is automatically and accurately obtained at the time of the event. Additionally, the processes of obtaining reference data and administering the medicament can be simplified and made convenient using the integrated receiver because of fewer loose parts (for example, cable, test strips, and the like) and less required manual data entry.

[0150] A battery 92 is operably connected to the microprocessor 82 and provides power for the receiver. In one embodiment, the battery is a standard AAA alkaline battery, however batteries can be used to power the system. In some embodiments, a power port (not shown) is provided permit recharging of rechargeable batteries. A quartz crystal 94 is operably connected to the microprocessor 168 and maintains system time for the computer system as a whole.

[0151] A PC communication (com) port 90 can be provided to enable communication with systems, for example, a serial communications port, allows for communicating with another computer system (for example, PC, PDA, server, or the like). In one exemplary embodiment, the receiver is able to download historical data to a physician's PC for retrospective analysis by the physician. The PC communication port 90 can also be used to interface with other medical devices, for example pacemakers, implanted analyte sensor patches, infusion devices, telemetry devices, or the like.

[0152] A user interface 96 comprises a keyboard 98, speaker 100, vibrator 102, backlight 104, liquid crystal display (LCD) 106, and/or one or more buttons 108. The components that comprise the user interface 96 provide controls to interact with the user. The keyboard 98 can allow, for example, input of user information about himself/herself, such as mealtime, exercise, insulin administration, and reference glucose values. The speaker 100 can provide, for example, audible signals or alerts for conditions such as present and/or predicted hyper- and hypoglycemic conditions. The vibrator 102 can provide, for example, tactile signals or alerts for reasons such as described with reference to the speaker, above. The backlight 104 can be provided, for example, to aid the user in reading the LCD in low light conditions. The LCD 106 can be provided, for example, to provide the user with visual data output. In some embodiments, the LCD is a touch-activated screen. The buttons 108 can provide for toggle, menu selection, option selection, mode selection, and reset, for example. In some alternative embodiments, a microphone can be provided to allow for voice-activated control.

[0153] The user interface 96, which is operably connected to the microprocessor 82 serves to provide data input and output for both the continuous glucose sensor, delivery mechanism, and/or for the single point glucose monitor.

[0154] In some embodiments, prompts or messages can be displayed on the user interface to guide the user through the initial calibration and sample measurement procedures for the single point glucose monitor. Additionally, prompts can be displayed to inform the user about necessary maintenance procedures, such as "Replace Sensing Membrane" or "Replace Battery." Even more, the glucose concentration value measured from the single point glucose monitor can be individually displayed.

[0155] In some embodiments, prompts or messages can be displayed on the user interface to convey information to the user, such as malfunction, outlier values, missed data transmissions, or the like, for the continuous glucose sensor. Additionally, prompts can be calibrated sensor glucose data can be displayed, which is described in more detail with reference U.S. Patent Applications 10/633,367 and 11/007,920.

[0156] In some embodiments, prompts or messages about the medicament delivery device can be displayed on the

user interface to inform or confirm to the user type, amount, and time of medicament delivery. In some embodiments, the user interface provides historical data and analytes pattern information about the medicament delivery, and the patient's metabolic response to that delivery, which can be useful to a patient or doctor in determining the level of effect of various medicaments.

[0157] Electronics 110 associated with the delivery device 16 (namely, the semi-automated and automated delivery devices) are operably connected to the microprocessor 82 and include a microprocessor 112 for processing data associated with the delivery device 16 and include at least a wired or wireless connection (for example, RF transceiver) 114 for transmission of data between the microprocessor 82 of the receiver 14 and the microprocessor 112 of the delivery device 16. Other electronics associated with any of the delivery devices cited herein, or other known delivery devices, can be implemented with the delivery device electronics 110 described herein, as is appreciated by one skilled in the art.

[0158] In some embodiments, the microprocessor 112 comprises programming for processing the delivery information in combination with the continuous sensor information. In some alternative embodiments, the microprocessor 82 comprises programming for processing the delivery information in combination with the continuous sensor information. In some embodiments, both microprocessors 82 and 112 mutually processor information related to each component.

[0159] In some embodiments, the medicament delivery device 16 further includes a user interface (not shown), which can include a display and/or buttons, for example. U.S. Patents 6,192,891, 5,536,249, and 6,471,689 describe some examples of incorporation of a user interface into a medicament delivery device, as is appreciated by one skilled in the art.

[0160] Electronics 116 associated with the single point glucose monitor 18 are operably connected to the microprocessor 120 and include a potentiostat 118 in one embodiment that measures a current flow produced at the working electrode when a biological sample is placed on the sensing membrane, such as described above. The current is then converted into an analog signal by a current to voltage converter, which can be inverted, level-shifted, and sent to an A/D converter. The microprocessor can set the analog gain via its control port (not shown). The A/D converter is preferably activated at one-second intervals. The microprocessor looks at the converter output with any number of pattern recognition algorithms known to those skilled in the art until a glucose peak is identified. A timer is then preferably activated for about 30 seconds at the end of difference is then divided by the value stored in the memory during instrument calibration and is then multiplied by the calibration glucose concentration. The glucose value in milligram per deciliter, millimoles per liter, or the like, is then stored in the microprocessor, displayed on the user interface, used to calibrate of the glucose sensor data stream, downloaded, and the like.

Programming and Processing (Draw Flow Diagrams)

[0161] Fig. 9 is a flow chart that illustrates the process 130 of validating therapy instructions prior to medicament delivery in one embodiment. In some embodiments, the therapy recommendations include a suggestion on the user interface of time, amount, and type of medicament to delivery. In some embodiments, therapy instructions include calculating a time, amount, and/or type of medicament delivery to administer, and optionally transmitting those instructions to the delivery device. In some embodiments, therapy instructions include that portion of a closed loop system wherein the determination and delivery of medicament is accomplished, as is appreciated by one skilled in the art.

[0162] Although computing and processing of data is increasingly complex and reliable, there are circumstances by which the therapy recommendations necessitate human intervention. Some examples include when a user is about to alter his/her metabolic state, for example due to behavior such as exercise, meal, pending manual medicament delivery, or the like. In such examples, the therapy recommendations determined by the programming may not have considered present or upcoming behavior, which may change the recommended therapy. Numerous such circumstances can be contrived, and a validation can be advantageous in order to ensure that therapy recommendations are appropriately administered.

[0163] At block 132, a sensor data receiving module, also referred to as the sensor data module, receives sensor data (e.g., a data stream), including one or more time-spaced sensor data points, from a sensor via the receiver, which can be in wired or wireless communication with the sensor. The sensor data point(s) can be raw or smoothed, such as described in U.S. Patent Application 10/648,849, entitled "SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM."

[0164] At block 134, a medicament calculation module, which is a part of a processor module, calculates a recommended medicament therapy based on the received sensor data. A variety of algorithms can be used to calculate a recommended therapy as is appreciated by one skilled in the art.

[0165] At block 136, a validation module, which is a part of the processor module, optionally validates the recommended therapy. The validation can include a request from the user, or from another component of the integrated system 10, for additional data to ensure safe and accurate medicament recommendation or delivery. In some embodiments, the validation requests the like. In some embodiments, the validation module is configured to request this information from the

user. In some embodiments, the validation module is responsive to a user inputting such information.

[0166] In some embodiments, when the integrated system 10 is in fully automated mode, the validation module is triggered when a potential risk is evaluated. For example, when a clinically risky discrepancy is evaluated, when the acceleration of the glucose value is changing or is low (indicative of a significant change in glucose trend), when it is near a normal meal, exercise or sleep time, when a medicament delivery is expected based on an individual's dosing patterns, and/or a variety of other such situations, wherein outside influences (meal time, exercise, regular medicament delivery, or the like) may deem consideration in the therapy instructions. These conditions for triggering the validation module can be pre-programmed and/or can be learned over time, for example, as the processor module monitors and patterns an individual's behavior patterns.

[0167] In some embodiments, when the integrated system 10 is in semi-automated mode, the system can be programmed to request additional information from the user regarding outside influences unknown to the integrated system prior to validation. For example, exercise, food or medicament intake, rest, or the like can be input into the receiver for incorporation into a parameter of the programming (algorithms) that processing the therapy recommendations.

[0168] At block 138, the receiver confirms and sends (for example, displays, transmits and/or delivers) the therapy recommendations, In manual integrations, the receiver can simply confirm and display the recommended therapy, for example. In semi-automated integrations, the receiver can confirm, transmit, and optionally delivery instructions to the delivery device regarding the recommended therapy, for example. In automated integrations the receiver can confirm and ensure the delivery of the recommended therapy, for example. These examples are not meant to be limiting and there are a variety of methods by which the receiver can confirm, display, transmit, and/or deliver the recommended therapy within the scope of the preferred embodiments.

[0169] Fig. 10 is a flow chart 140 that illustrates the process of providing adaptive metabolic control using an integrated system in one embodiment. In this embodiment, the integrated system is programmed to learn the patterns of the individual's metabolisms, including metabolic response to medicament delivery.

[0170] At block 142, a medicament data receiving module, which can be programmed within the receiver 14 and/or medicament delivery device 16, receives medicament delivery data, including time, amount, and/or type. In some embodiments, the user is prompted to input medicament delivery information into the user interface. In some embodiments, the medicament delivery device 16 sends the medicament delivery data to the medicament data-receiving module. data module, receives sensor data (e.g., a data stream), including one or more time-spaced sensor data points, from a sensor via the receiver, which can be in wired or wireless communication with the sensor.

[0171] At block 146, the processor module, which can be programmed into the receiver 14 and/or the delivery device 16 is programmed to monitor the sensor data from the sensor data module 142 and medicament delivery from the medicament delivery module 144 to determine an individual's metabolic profile, including their response to various times, amounts, and/or types of medicaments. The processor module uses any pattern recognition-type algorithm as is appreciated by one skilled in the art to quantify the individual's metabolic profile.

[0172] At block 148, a medicament calculation module, which is a part of a processor module, calculates the recommended medicament based on the sensor glucose data, medicament delivery data, and/or individual's metabolic profile. In some embodiments, the recommended therapy is validated such as described with reference to Fig. 9 above. In some embodiments, the recommended therapy is manually, semi-automatically, or automatically delivered to the patient.

[0173] At block 150, the process of monitoring and evaluation a patient's metabolic profile is repeated with new medicament delivery data, wherein the processor monitors the sensor data with the associated medicament delivery data to determine the individual's metabolic response in order to adaptively adjust, if necessary, to newly determined metabolic profile or patterns. This process can be continuous throughout the life of the integrated system, can be initiated based on conditions met by the continuous glucose sensor, can be triggered by a patient or doctor, or can be provided during a start-up or learning phase.

[0174] While not wishing to be bound by theory, it is believed that by adaptively adjusting the medicament delivery based on an individual's metabolic profile, including response to medicaments, improved long-term patient care and overall health can be achieved.

[0175] Fig. 11 is a flow chart 152 that illustrates the process of glucose signal estimation using the integrated sensor and medicament delivery device in one embodiment. Glucose estimation and/or prediction are described in U.S. Patent Applications 10/633,367 and 11/007,920. However, the preferred embodiments described herein, further incorporated additional data of medicament delivery in estimating or predicting glucose trends.

[0176] At block 154, a sensor data receiving module, also referred to as the sensor data module, receives sensor data (e.g., a data stream), including one or more time-spaced sensor data points, from a sensor via the receiver, which can be in wired or wireless communication with the sensor.

programmed within the receiver 14 and/or medicament delivery device 16, receives medicament delivery data, including time, amount, and/or type.

[0177] At block 158, the processor module evaluates medicament delivery data with substantially time corresponding glucose sensor data to determine individual metabolic patterns associated with medicament delivery. "Substantially time

corresponding data" refers to that time period during which the medicament is delivered and its period of release in the host.

[0178] At block 160, the processor module estimates glucose values responsive to individual metabolic patterns associated with the medicament delivery. Namely, the individual metabolic patterns associated with the medicament delivery are incorporated into the algorithms that estimate present and future glucose values, which are believed to increase accuracy of long-term glucose estimation.

Examples

[0179] In one exemplary implementation of the preferred embodiments, the continuous glucose sensor (and its receiver) comprises programming to track a patient during hypoglycemic or near-hypoglycemic conditions. In this implementation, the processor includes programming that sends instructions to administer a hypoglycemic treating medicament, such as glucagon, via an implantable pump or the like, when the glucose level and rate of change surpass a predetermined threshold (for example, 80 mg/dL and 2 mg/dL/min). In this situation, the sensor waits a predetermined amount of time (for example, 40 minutes), while monitoring the glucose level, rate of change of glucose, and/or acceleration/deceleration of glucose in the patient, wherein if the rate of change and/or acceleration shows a changing trend away from hypoglycemia (for example, decreased deceleration of glucose levels to non-hypoglycemia), then the patient need not be alarmed. In this way, the automated glucagon delivery device can proactively preempt hypoglycemic conditions without alerting or awaking the patient.

[0180] In another exemplary implementation of the preferred embodiments, a continuous glucose sensor is integrated with a continuous medicament delivery device (for example, an insulin pump) and a bolus medicament delivery device (for example, and insulin pen). In this embodiment, the integration takes exploits the benefits of automated and semi-automated device, for example, providing an automated integration with an infusion pump, while provide semi-automated integration with an insulin pen as necessary.

[0181] In yet another exemplary implementation of the preferred embodiments, a medicament delivery device is provided that includes reservoirs of both fast acting insulin and slow acting insulin. The medicament delivery device is integrated with the receiver as described elsewhere herein; however in this implementation, the receiver determines an amount of fast acting configured to mix slow-acting and fast-acting insulin in the amounts provided. In this way, the receiver and medicament delivery device can work together in a feedback loop to iteratively optimize amounts of slow and fast acting insulin for a variety of situations (for example, based on glucose level, rate of change, acceleration, and behavioral factors such as diet, exercise, time of day, and the like) adapted to the individual patient's metabolic profile.

[0182] In yet another exemplary implementation of the preferred embodiments, an integrated hypo- and hyper-glycemic treating system is provided. In this implementation, a manual- , semi-automated, or automated integration of an insulin delivery device is combined with a manual-, semi-automated, or automated integration of a glucose or glucagon delivery device. These devices are integrated with the receiver for the continuous glucose sensor in any manner described elsewhere herein. While not wishing to be bound by theory, it is believed that the combination of a continuous glucose sensor, integrated insulin device, and integrated glucose or glucagon device provides a simplified, comprehensive, user friendly, convenient, long-term and continuous method of monitoring, treating, and optimizing comprehensive care for diabetes.

[0183] Methods and devices that can be suitable for use in conjunction with aspects of the preferred embodiments are disclosed in several pending applications including U.S. Application No. 10/695,636 filed October 28, 2003 and entitled, "SILICONE COMPOSITION FOR BIOCOMPATIBLE MEMBRANE"; U.S. Patent Application No. 10/648,849 entitled, "SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM," filed August 22, 2003; U.S. Patent Application No. 10/646,333 entitled, "OPTIMIZED SENSOR GEOMETRY FOR AN IMPLANTABLE GLUCOSE SENSOR," filed August 22, 2003; U.S. Patent Application No. 10/647,065 entitled, "POROUS MEMBRANES FOR USE WITH IMPLANTABLE DEVICES," filed August 22,2003; U.S. Patent Application Nos. 10/633,367, 10/632,537, 10/633,404, and 10/633,329, each entitled, "SYSTEM AND METHODS FOR PROCESSING ANALYTE SENSOR DATA," filed August 1, 2003; and U.S. Patent Application No. 09/447,227 filed November 22, 1999 and entitled "DEVICE AND METHOD FOR DETERMINING ANALYTE LEVELS"; and several published applications including U.S. 2003-0032874; U.S. 2003-0217966; and U.S. 2004-0011671; as well as issued patents including U.S. 6,001,067; U.S. 4,994,167; U.S. 4,757,022; U.S. 6,702,857; U.S. 6,741,877; and U.S. 6,558,321.

[0184] The term "comprising" as used herein is synonymous with "including," "containing," or "characterized by," and is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

[0185] All numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0186] The above description discloses several methods and materials of the present invention. This invention is

susceptible to modifications in the methods and materials, as well as alterations in the fabrication methods and equipment. Such modifications will become apparent to those skilled in the art from a consideration of this disclosure or practice of the invention disclosed herein. Consequently, it is not intended that this invention be limited to the specific embodiments disclosed herein, but that it cover all modifications and alternatives coming within the true scope and spirit of the invention as embodied in the attached claims.

The invention may be further described with reference to the following clauses:

1. A method for managing diabetes, the method comprising:

receiving in a receiver a data stream from an integrated glucose sensor, the data stream comprising at least one sensor data point;
calculating a medicament therapy recommendation responsive to the sensor data point;
assessing the calculated medicament therapy based on at least one of data input into the receiver and data obtained from an integrated single point glucose monitor, to yield an assessment result; and
outputting information based on the assessment result, wherein the information is employed in the management of diabetes.

2. The method according to Clause 1, wherein the output step comprises outputting the medicament therapy recommendation to a user interface after confirmation of a therapy decision by a user when the assessment result is indicative of a failed validation.

3. The method according to Clause 1, wherein the output step includes outputting the medicament therapy recommendation to a user interface when the assessment result is indicative of a successful validation.

4. The method of Clause 3, wherein the output step comprises displaying the medicament therapy recommendation on at least one of a receiver user interface and a medicament delivery device user interface.

5. The method according to Clause 1, wherein the output step comprises transmitting the medicament therapy recommendation to a medicament delivery device.

6. The method according to Clause 1, wherein the output step comprises delivering a medicament according to the medicament therapy recommendation via an automated delivery device.

7. A method for managing diabetes in a host, the method comprising:

receiving in a receiver medicament delivery data responsive to a medicament delivery from a medicament delivery device;
receiving, in a receiver, a data stream from an integrated glucose sensor, the data stream comprising at least one sensor data point obtained before the medicament delivery or after the medicament delivery;
determining a metabolic response of the host to the medicament delivery;
receiving a subsequent data stream from the integrated glucose sensor, the data stream comprising at least one subsequent sensor data point; and
metabolic response to the medicament delivery, wherein the medicament therapy recommendation is employed in managing diabetes in the host.

8. A method for estimating a glucose level, the method comprising:

receiving in a receiver a data stream from an integrated glucose sensor, the data stream comprising at least one sensor data point;
receiving, in a receiver, medicament delivery data responsive to a medicament delivery from a medicament delivery device;
determining a metabolic response of a host associated with the medicament delivery by evaluating the medicament delivery data using glucose sensor data correlated with times of delivery and release of the medicament delivery; and
estimating a glucose level responsive to the metabolic response associated with the medicament delivery.

9. The method according to Clauses 7 or 8, wherein the metabolic response is calculated using a pattern recognition algorithm.

10. The method according to Clause 7 or 8, wherein the step of determining a metabolic response is repeated when additional medicament delivery data is received by the receiver.

11. The method according to Clause 10, wherein the metabolic response is iteratively determined for a time period exceeding one week.

12. An integrated system for monitoring and treating diabetes, the system comprising:

a glucose sensor, wherein the glucose sensor is configured to substantially continuously measure glucose in a host, and is configured to output a data stream comprising at least one sensor data point;
a receiver operably connected to the glucose sensor, wherein the receiver is configured to receive the data stream; and
a medicament delivery device, wherein the delivery device is at least one of physically connected to the receiver and operably connected to the receiver.

13. The integrated system according to Clause 12, wherein the glucose sensor comprises an implantable glucose sensor.
14. The integrated system according to Clause 12, wherein the glucose sensor comprises a long-term subcutaneously implantable glucose sensor.
15. The integrated system according to Clause 12, wherein the medicament delivery device comprises a syringe detachably connectable to the receiver.
16. The integrated system according to clause 12, wherein the medicament delivery device comprises at least one transdermal patch detachably connectable to the receiver.
device comprises an inhaler delivery device or a spray delivery device, wherein the delivery device is detachably connectable to the receiver.
18. The integrated system according to Clause 12, wherein the medicament delivery device comprises a pen-type injector or a jet-type injector.
19. The integrated system according to Clause 12, wherein the medicament delivery device comprises a transdermal pump.
20. The integrated system according to Clause 12, wherein the medicament delivery device comprises an implantable pump.
21. The integrated system according to Clause 12, wherein the medicament delivery device comprises a manual implantable pump.
22. The integrated system according to Clause 12, wherein the medicament delivery device comprises a cell transplantation device.
23. The integrated system according to Clause 12, wherein the medicament delivery device is detachably connected to the receiver.
24. The integrated system according to Clause 12, wherein the medicament delivery device is operably connected to the receiver by a wireless connection.
25. The integrated system according to Clause 12, wherein the medicament delivery device is operably connected to the receiver by a wired connection.
26. The integrated system according to Clause 12, further comprising a single point glucose monitor, wherein the single point glucose monitor is at least one of physically connected to the receiver and operably connected to the receiver.
27. The integrated system according to Clause 26, wherein the glucose sensor comprises an enzyme membrane system for electrochemical detection of glucose, and wherein the single point glucose monitor comprises an enzyme membrane system for electrochemical detection of glucose.
28. The integrated system according to Clause 12, wherein the receiver comprises a microprocessor, and wherein the microprocessor comprises programming for calculating and outputting a medicament delivery instruction.
29. The integrated system according to Clause 28, wherein the microprocessor further comprises a validation module that validates a medicament delivery instruction prior to outputting the medicament delivery instruction.
30. The integrated system according to Clause 2, wherein the receiver is configured to receive, for a first time period, medicament delivery data responsive to medicament delivery from the medicament delivery device.
31. The integrated system according to Clause 30, wherein the receiver comprises a microprocessor, and wherein the microprocessor comprises programming to determine a metabolic substantially corresponding to a time of delivery or release of the medicament to the host.
32. The integrated system according to Clause 31, wherein the microprocessor calculates a medicament therapy recommendation for a second time period responsive to the sensor data and the metabolic response.
33. The integrated system according to Clause 31, wherein the microprocessor comprises programming to estimate a glucose value responsive to glucose sensor data and a metabolic response of a host.
34. The integrated system according to Clause 12, wherein the glucose sensor is configured to substantially continuously measure glucose in a host for a time period exceeding one week.
35. The integrated system according to Clause 12, wherein the glucose sensor is configured to substantially continuously measure glucose in a host for a time period from about two days to about one week.
36. An integrated system for monitoring and/or treating diabetes as substantially described in the examples presented herein.

Claims

1. A method for treating diabetes with an integrated glucose sensor and medicament delivery device, the method comprising:

receiving sensor data from a glucose sensor, the sensor data comprising one or more sensor data points;
calculating a medicament therapy recommendation based at least in part on the sensor data;
validating the calculated therapy recommendation based on data input into a receiver, data obtained from a single point glucose monitor, or combinations thereof; and
outputting information reflective of the calculated therapy recommendation responsive to a validated calculated therapy recommendation.

2. The method according to claim 1, further comprising detecting impending clinical risk.

3. The method according to claim 1, wherein outputting information comprises outputting the calculated therapy recommendation to a user interface.

4. The method according to claim 1, wherein outputting information comprises transmitting the calculated therapy recommendation to a medicament delivery device.

6. The method according to claim 1, wherein outputting information comprises delivering the calculated therapy recommendation via a medicament delivery device.

7. The method according to claim 1, wherein the calculating is further based on the data input into a receiver, the data obtained from a single point glucose monitor, or the combinations thereof.

8. An integrated system for monitoring and treating diabetes, the system comprising:

a glucose sensor, wherein the glucose sensor substantially continuously measures glucose in a host for a period exceeding one hour, and outputs a data stream, including one or more sensor data points;
a receiver operably connected to the glucose sensor, wherein the receiver is configured to receive the data stream; and
a medicament delivery device, wherein the delivery device is at least one of physically or operably connectable to the receiver, wherein the receiver comprises a processor, and wherein the processor comprises programming configured to calculate and output medicament delivery instructions, and wherein the processor further comprises programming configured to validate the medicament delivery instructions by prompting a user to provide a biological sample from a single point glucose monitor and by validating the medicament delivery instructions responsive to data obtained from the single point glucose monitor.

9. The integrated system according to claim 8, wherein the medicament delivery device comprises at least one device selected from the group consisting of an inhaler, a spray device, a pen, jet-type injector, a transdermal pump, an implantable pump, and combinations thereof.

10. The integrated system according to claim 8, wherein the processor comprises programming configured to automatically run the programming configured to validate the medicament delivery instructions when a rate of acceleration or deceleration of the sensor data is outside a predetermined range.

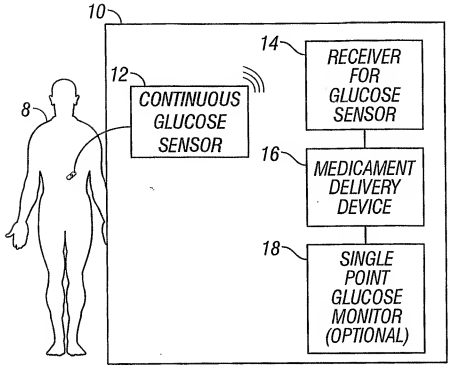
11. The integrated system according to claim 8, wherein the processor comprises programming configured to automatically run the validation module programming configured to validate the medicament delivery instructions when a rate of change of the sensor data is outside a predetermined range.

12. The integrated system according to claim 8, wherein the programming configured to validate the medicament delivery instructions comprises programming configured to request information, wherein the information requested comprises at least one item of information selected from the group consisting of: time of day, meals, meal time, regular medicament delivery, sleep, calories, carbohydrates, exercise, sickness, and combinations thereof.

13. The integrated system according to claim 8, wherein the single point glucose monitor is detachably connectable to the receiver.

14. The integrated system according to claim 8, wherein the single point glucose monitor is operably connectable to the receiver by a wired connection.

15. The integrated system according to claim 8, wherein the single point glucose monitor is operably connectable to the receiver by a wireless connection.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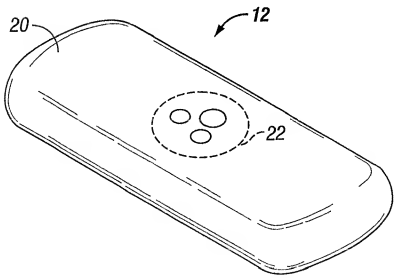
14
RECEIVER FOR GLUCOSE SENSOR
12
CONTINUOUS GLUCOSE SENSOR
8
16
MEDICAMENT DELIVERY DEVICE
18
SINGLE POINT GLUCOSE MONITOR (OPTIONAL)

FIG. 1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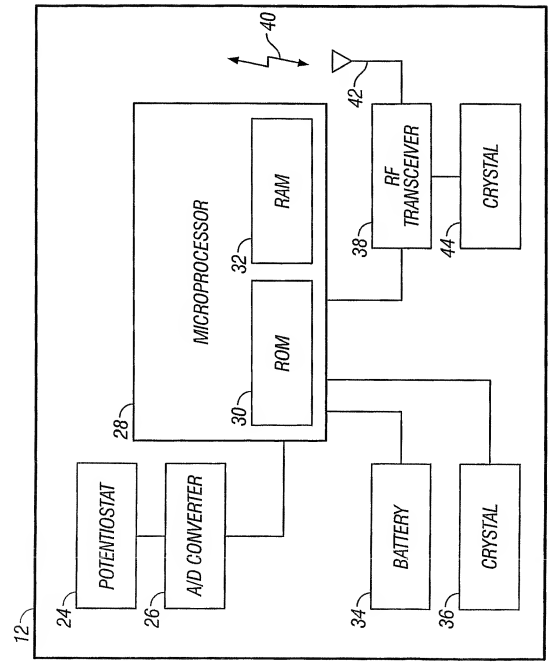
12
22

FIG. 2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24
POTENTIOSTAT
26
A/D CONVERTER
28
MICROPROCESSOR
30
ROM
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RAM
34
BATTERY
36
CRYSTAL
38
RF TRANSCEIVER
40
42
44
CRYSTAL

FIG. 3

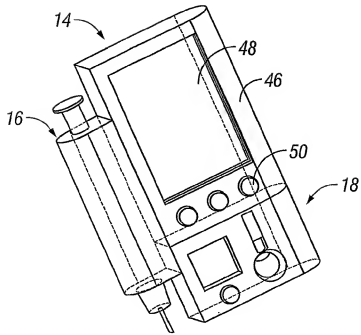


FIG. 4A

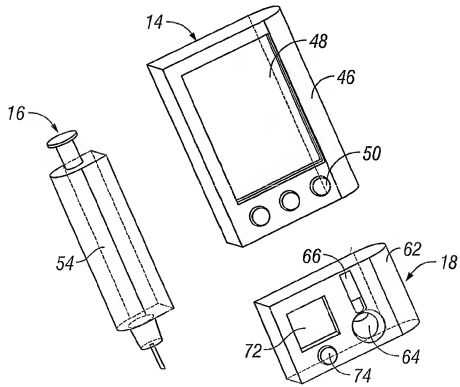


FIG. 4B

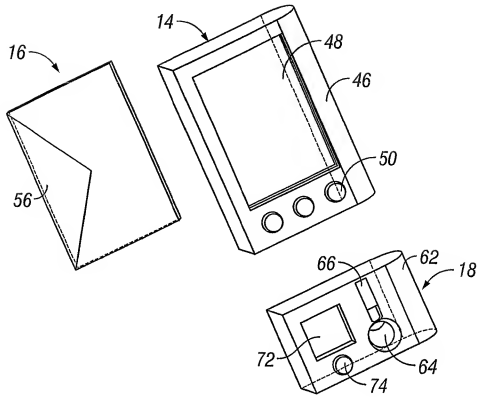


FIG. 5A

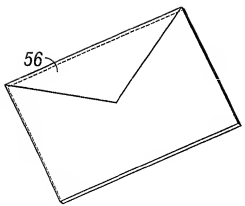


FIG. 5B

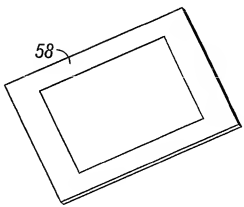


FIG. 5C

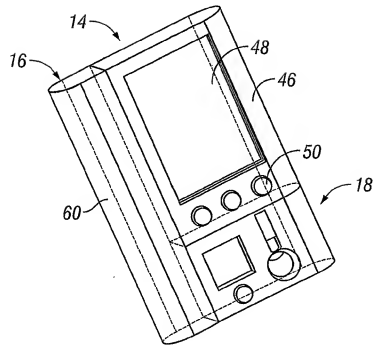


FIG. 6A

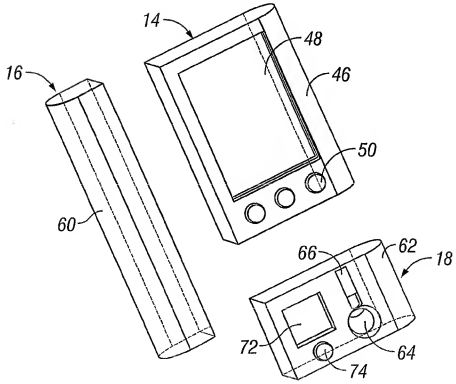


FIG. 6B

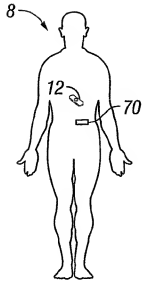


FIG. 7A

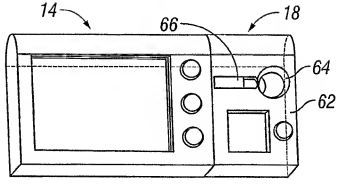


FIG. 7B

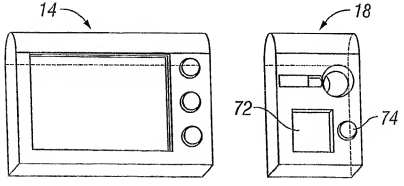
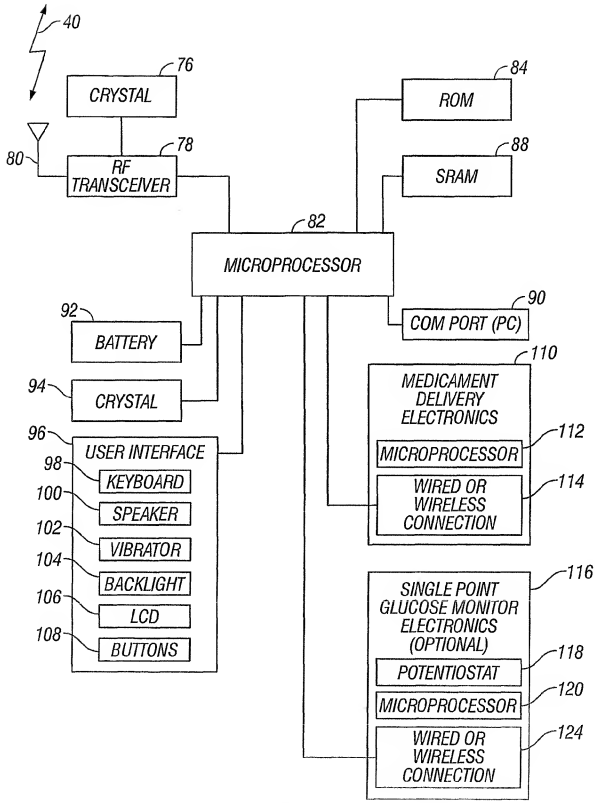


FIG. 7C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76
CRYSTAL
84
ROM
80
78
RF TRANSCEIVER
88
SRAM
82
MICROPROCESSOR
92
BATTERY
90
COM PORT (PC)
110
MEDICAMENT DELIVERY ELECTRONICS
94
CRYSTAL
112
MICROPROCESSOR
114
WIRED OR WIRELESS CONNECTION
96
USER INTERFACE
98
KEYBOARD
100
SPEAKER
102
VIBRATOR
104
BACKLIGHT
106
LCD
108
BUTTONS
116
SINGLE POINT GLUCOSE MONITOR ELECTRONICS (OPTIONAL)
118
POTENTIOSTAT
120
MICROPROCESSOR
124
WIRED OR WIRELESS CONNECTION

FIG. 8

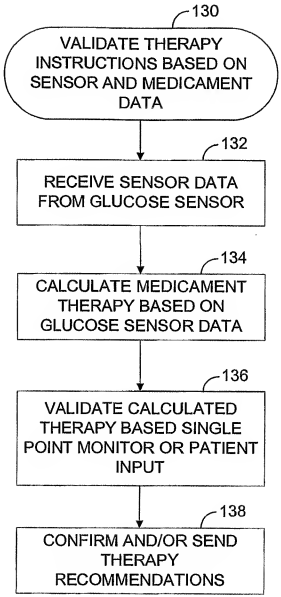
130
VALIDATE THERAPY INSTRUCTIONS BASED ON SENSOR AND MEDICAMENT DATA
132
RECEIVE SENSOR DATA FROM GLUCOSE SENSOR
134
CALCULATE MEDICAMENT THERAPY BASED ON GLUCOSE SENSOR DATA
136
VALIDATE CALCULATED THERAPY BASED SINGLE POINT MONITOR OR PATIENT INPUT
138
CONFIRM AND/OR SEND THERAPY RECOMMENDATIONS

FIG. 9

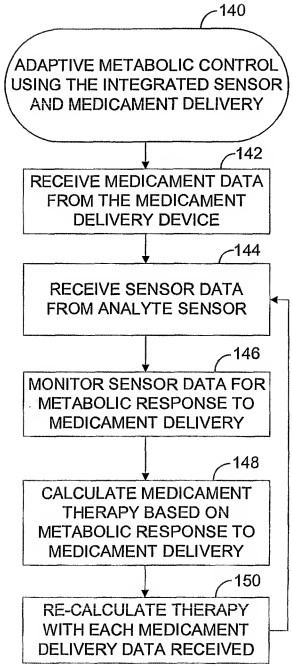
140
ADAPTIVE METABOLIC CONTROL USING THE INTEGRATED SENSOR AND MEDICAMENT DELIVERY
142
RECEIVE MEDICAMENT DATA FROM THE MEDICAMENT DELIVERY DEVICE
144
RECEIVE SENSOR DATA FROM ANALYTE SENSOR
146
MONITOR SENSOR DATA FOR METABOLIC RESPONSE TO MEDICAMENT DELIVERY
148
CALCULATE MEDICAMENT THERAPY BASED ON METABOLIC RESPONSE TO MEDICAMENT DELIVERY
150
RE-CALCULATE THERAPY WITH EACH MEDICAMENT DELIVERY DATA RECEIVED

FIG. 10

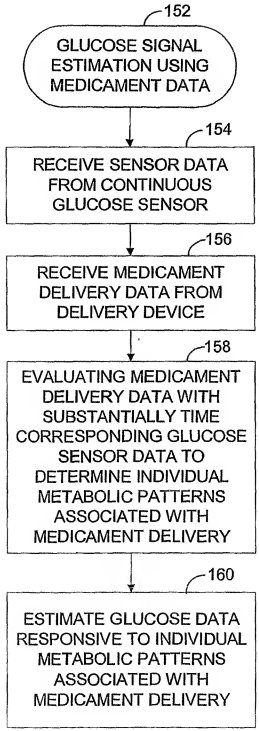
152
GLUCOSE SIGNAL ESTIMATION USING MEDICAMENT DATA
154
RECEIVE SENSOR DATA FROM CONTINUOUS GLUCOSE SENSOR
156
RECEIVE MEDICAMENT DELIVERY DATA FROM DELIVERY DEVICE
158
EVALUATING MEDICAMENT DELIVERY DATA WITH SUBSTANTIALLY TIME CORRESPONDING GLUCOSE SENSOR DATA TO DETERMINE INDIVIDUAL METABOLIC PATTERNS ASSOCIATED WITH MEDICAMENT DELIVERY
160
ESTIMATE GLUCOSE DATA RESPONSIVE TO INDIVIDUAL METABOLIC PATTERNS ASSOCIATED WITH MEDICAMENT DELIVERY

FIG. 11

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EUROPEAN SEARCH REPORT

Application Number
EP 10 16 3654

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	23 July 2010	Rodríguez Cossío, J

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